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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,837	SUZUKI ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☒ Claim(s) *1-3 and 7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. Claims 1-3, and 7 are objected to because of the following informalities: With regard to Claim 1 "adapter" is spelt "adaptor". With regard to Claim 2, Lines 11-12 are unclear, it seems to be a parentheses missing. With regard to Claim 3, "are identical ones" is grammatically incorrect. With regard to Claim 7 the use of "of" before biatin, FIGT, and DIG is grammatically incorrect. With regard to Claim 7, "biotin" is spelt "biatin". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-9 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9 provides for the use of the processes of mRNA isolation, polyA addition, cDNA synthesis, cDNA processing, PCR, electrophoresis process, Fragment recovery, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-9 is unclear whether directed to analyzing prokaryotic expression or a method for cDNA recovery. The preamble states a method of analyzing prokaryotic gene expression. The last steps teach a process of cDNA fragment recovery. Therefore it is unclear whether the method is intended to be drawn to a method of analyzing prokaryotic gene expression or cDNA fragment recovery.

Claim 2 and 3 are indefinite because it is not clear what "the hybrid" is referring to in the claim. Claim 2 is drawn to a process of hybridizing a first nucleotide to a portion of the 16S rRNA and hybridizing a second nucleotide to a portion of the 23S rRNA. A tag substance hybridized to a third nucleotide is then hybridized to a different region of the 16S rRNA and a tag substance is hybridized to a fourth nucleotide which is then hybridized to a different region of the 23S rRNA. Then there is a process of removing "the hybrid" of the 16S and "the hybrid" of the 23S. It is unclear which hybrid, "the hybrid" is referring to in the proceeding steps. It is unclear if "the hybrid" is the hybrid of the 16S rRNA and the first nucleotide OR the 16S rRNA and the third tagged nucleotide. The same is unclear for the 23S rRNA region. It is unclear which hybrid, "the hybrid" is referring to in the proceeding steps. It is unclear if "the hybrid" is the hybrid of the 23S rRNA and the second nucleotide OR the 23S rRNA and the fourth tagged nucleotide.

Claims 2 and 3 are indefinite because it is unclear if the first tag substance is hybridized to a third nucleotide or to the 16S rRNA. It is unclear whether the second tag substance is added to the fourth nucleotide or to the 23S rRNA.

Claim 2 and 3 are indefinite because it is unclear what the final step is in the sequence. The claim is drawn to an mRNA isolation process comprising hybridizing probes to the 16S rRNA and 23S rRNA regions, removing the 16S rRNA and 23S rRNA regions. It is unclear if the final part of the step is the removed rRNA regions and if so how to get back to the preamble of isolating mRNA.

Claim 6 is unclear because it is confusing if both of the primers have a marker substance or one of the primers has a marker substance.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

In order to efficiently describe the art rejections presented the examiner has labeled each step of Claim 1 in order to make the art rejection easier to follow.

CLAIM 1: 1A: an mRNA isolation process for isolating an mRNA from a prokaryotic cell

1B: a polyA addition process for adding a polyA at the 3' end of the mRNA

1C: a cDNA synthesis process for synthesizing a cDNA from the polyA-added mRNA

1D: a cDNA processing process for preparing an adaptor attached cDNA fragment having the sequence of the first adapter at one end and the sequence of a second adapter at the other end

1E: a first PCR process for performing PCR with the adaptor-attached cDNA fragments, using a first primer having a sequence complementary to the sequence of the first adaptor and a second primer having a sequence complementary to the sequence of the second adaptor

1F: an electrophoresis process

1G: a cDNA fragment recovery process

4. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weissman et al. (US Patent 5712126 January 27, 1998) in view of Wendisch et al. (Analytical Biochemistry 2001 Vol. 290 p. 205).

Weissman et al. teaches a method to analyze gene expression by selective PCR amplification and display of 3'end restriction fragments of double stranded cDNAs (Abstract). With regard to Claim 1C, Weissman et al. teaches cDNA synthesis from a polyA tailed mRNA (Figure 1 step 1). With regard to Claim 1D, Weissman et al. teaches a cDNA with a first and second adapter attaches (Figure 1, steps 4 and 5). With regard to Claim 1E, Weissman et al. teaches a PCR cycling method (Figure 1 step 6). Weissman et al. teaches two primers attached to the first and second adapters (Figure 1, Step 5). With regard to Claim 1F, Weissman et al. teaches the PCR products were analyzed on a 6% polyacrylamide sequencing gel (Column 5, lines 60-62). With regard to Claim 1G, Weissman et al. teaches cDNA fragment was recovered by cutting by a single or multiple restriction enzymes, extracting the bands from the display gel, and subcloning into a pCRscript to obtain plasmids (Column 6, lines 5-10).

Weissman et al., however, does not use mRNA from a prokaryotic gene (Claim 1A and B).

Wendisch et al. teaches a method to add polyadenylate (polyA) to extracted E. Coli (prokaryote) (Abstract). With regard to Claim 1A, Wendisch et al. teaches isolating a population of cellular mRNAs in crude cell extracts by mechanical lysis (p. 205 2nd column last paragraph last full sentence). With regard to Claim 1B, Wendisch et al. teaches the mRNA was polyadenylated with poly(a) polymerase I (p. 205 2nd column last full sentence).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Weissman et al. to use

polyA-prokaryotic mRNA as taught by Wendisch et al. The ordinary artisan would have been motivated to modify the method of Weissman et al. to use polyA-prokaryotic mRNA because Wendisch et al. teaches that bacterial mRNAs are not uniformly polyadenylated and cannot be distinguished from rRNA or tRNA (p. 205 2nd column 1st line 2nd paragraph). Wendisch et al. teaches that polyadenylated RNA will increase the signal intensities in gene expression studies because the mRNA is enriched (p. 213 last paragraph). The ordinary artisan would want to enrich the mRNA in order to produce sufficient signal intensity for gene expression studies.

5. Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissman et al. (US Patent 5712126 January 27, 1998) in view of Wendisch et al. (Analytical Biochemistry 2001 Vol. 290 p. 205) as applied to claim 1 above, and further in view of Alland et al. (US Patent October 1, 2002) and Shah et al. (Journal of Clinical Microbiology November 1994 Vol 32 p. 2718).

Neither Weissman et al. or Wendisch et al. teach a process of hybridizing a 16S and 23S rRNA region simultaneously.

Alland et al. teaches a method of identifying differentially expressed mRNA (Abstract). Allan et al. teaches removing rRNA from an amplification library in order to isolate mRNA (Column 7, lines 1-5). Alland et al. teaches using PCR probes to the 16S and 23S genes (Column 7, lines 8-9). Alland et al. teaches labeling the PCR probes with a detectable marker such as florescence, enzymes, and radiolabeled such as isotopes and biotin (Column 4, lines 5-10). Alland et al. teaches removing the cosmids

(which would include the 16S and 23S probes and the nucleotide tags) by SDS lysis (column 7, lines 10-15).

Shah et al. teaches a method of a sensitive, nonisotopic hybridization assay (Abstract). With regard to Claim 2, Shah et al. teaches an assay to detect Chlamydia trachomatis rRNA (Abstract). Shah et al. teaches the transcribed rRNA contained the 16S region as well as a partial portion of the 23S region (p. 2719 1st paragraph). Shah et al. teaches to assay with two types of probes a test-specific capture probe which complexes with a magnetic bead (a tag) and a detector molecule by Q-Beta replicase in the presence of propidium iodide (Abstract). Shah et al. teaches the magnetic bead Shah et al. teaches hybridizing the detector probe and the magnetic tag probe (Figure 1 p. 2719). Shah et al. teaches the magnetic tag probe has a dA-tail which hybridizes to the target (nucleotide labeled with a magnetic which hybridizes to a region of the rRNA). Shah et al. teaches that the target-detector probe hybrid was released from the solid support and is dissociated (p. 2720 2nd column).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Weissman et al. and Wendisch et al. to incorporate enrichment of mRNA using probes attached to the 16S and 23S rRNA region as taught by Alland et al. and Shah et al. Alland teaches a rapid method of identifying differentially expressed mRNA to help understand gene differential gene expression (Column 1, lines 29-31). Alland et al. teaches a method of removing unwanted nucleic acids (Column 3, lines 52-53). Allan et al. teaches a method to study the differences in mRNA expression by removing abundant rRNA sequences which

confound the expression detection of mRNA (Column 3, lines 15-31). Alland teaches without removing rRNA expression differentially expressed genes can only be identified where large amounts of RNA can be obtained (Column 1, lines 14-16). Alland et al. teaches large amounts of RNA makes using array technology difficult (Column 1, lines 19-21). Alland et al. teaches current techniques to study differential gene expression in bacteria are limited by problems associated with separating abundant rRNA sequences from mRNA and the method describes a simple and novel method for studying differential gene regulating between two bacterial populations (Column 13, lines 66-67 and Column 14 lines 1-6). Alland et al. teaches a method of using two probes to detect the 16S and 23S regions and remove the rRNA from the mRNA, however, it involves the extra steps of creating a cosmid library to detect rRNA. Allan et al. teaches that the nucleic acid probes may be labeled with detectable markers which permits detection of unwanted nucleic acids upon hybridization (Column 4, lines 4-6). Shah et al. teaches a method to attach magnetic beads (a label) to probes in order to separate the hybridized area from a solution. The ordinary artisan would be motivated to use the enrichment for mRNA method of Shah et al. because the use of magnetic beads would alleviate the requirement for generating cosmids and would speed up the isolation process. Shah et al. teaches a method that is rapid and specifically detects very low levels of target nucleic acids (Abstract), therefore the method of Alland et al. would be modified by the teachings of a magnetic bead as taught by Shah et al. would increase the specificity and make the isolation method more rapid. Instead of creating a cosmid library to detect rRNA and then lysing the detected rRNA, the method would be done in a quick

assay that involves labeling the rRNA with a magnetic bead to pull it from solution. The ordinary artisan would be motivated to probe both the 16S and 23S regions to remove the regions from the mRNA because Alland et al. teaches these regions confound mRNA expression studies. The ordinary artisan would further be motivated to label the 16S and 23S regions with a magnetic bead in order to quickly separate the rRNA from the mRNA.

6. Claims 4-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissman et al. (US Patent 5712126 January 27, 1998) in view of Wendisch et al. (Analytical Biochemistry 2001 Vol. 290 p. 205) as applied to claim 1 above, and further in view of Belyavsky et al. (US Patent 6120996 September 19, 2000).

Neither Weissman et al. or Wendisch et al. teach a process of cDNA synthesis with a tag substance, restriction enzymes, and a high-affinity substance, or using markers on both primers, a second PCR after cDNA recovery, or cutting out the gel to litigate and clone in E. Coli.

Belyavsky et al. teaches a method of identification of differentially expressed mRNA which consists of synthesizing from a set of sequences of mRNA sets of fragments of complementary cDNA that are separated and differential signal intensity is identified (Abstract). With regard to Claim 4 and 7, Belyavsky et al. teaches attaching a 5' biotin group to the cDNA and is bonded to a streptavidin-containing solid support (column 5 lines 1-5 and 15-18). Belyavsky et al. teaches cleaving the cDNA with a restriction enzyme such as Sau3A (Type 1 Restriction enzyme) (Column 5, lines 10-15).

Belyavsky et al. teaches amplifying the fragments of cDNA by means of a PCR with a primer that is in the adaptor and modified with a biotin group (Column 5, lines 20-24). With regard to Claim 6, Belyavsky et al. teaches a label is added to the 3' primer (Column 5 lines 27-30), therefore Belyavsky et al. teaches a biotin label on one primer and a radioactive label on the other primer. Belyavsky et al. teaches the cDNA goes through sequential exhaustive cleavage with 8-10 restrictions carried out with restriction of 6-letter, 5-letter, and 4-letter restriction sites (Column 5 lines 35-40). Belyavsky et al. teaches that cleavage is done with EcoRV (type II restriction enzyme) (Column 8 lines 40-45). Belyavsky et al. teaches the labeled fragments are release and separated (Column 5, lines 35-45). Belyavsky et al. teaches the cDNA fragment is eluted from the gel and is amplified by means of PCR using adapter primers (Column 6, lines 9-12). With regard to Claim 5, Belyavsky et al. teaches that the fragments are cut out of the gel and eluted by incubation (Column 8, lines 54-56). Belyavsky et al. teaches the amplified fragment is cloned into a plasmid or phage vector (Column 6, lines 15-18). With regard to Claim 8, Belyavsky et al. teaches the amplified fragment is ligated to plasmid vector pUC18 (an e.coli phagemid) (Column 8, line 67 and Column 9 line 1).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Weissman et al. and Wendisch et al. to incorporate a process of cDNA synthesis with a tag substance, restriction enzymes, and a high-affinity substance, or using markers on both primers, a second PCR after cDNA recovery, or cutting out the gel to litigate and clone in E. Coli as taught by Belyavsky et al. The ordinary artisan would have been motivated to modify

the method of Weissman et al. and Wendisch et al. to incorporate a process of cDNA synthesis with a tag substance, restriction enzymes, and a high-affinity substance, or using markers on both primers, a second PCR after cDNA recovery, or cutting out the gel to litigate and clone in E. Coli as taught by Belyavsky et al. because Belyavsky et al. teaches a method to detect mRNA sequences with an increase of sensitivity and for unambiguous identification of individual fragments of cDNA (Column 3, lines 45-50). The ordinary artisan would use the cDNA fragmenting and cloning technique taught by Belyavsky et al. because Belyavsky et al. teaches the intensity of the signal from each fragment of cDNA varies dependent on the proportion of mRNA in the different cells therefore this method allows for the increased sensitivity of detecting cDNA fragments by amplifying by means of restriction and cloning (Column 3, lines 50-65).

Conclusion

7. No Claims are allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon 6/09/06

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